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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,578	03/09/2001	Patrick Hwu	2026-4341	6841

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EXAMINER
LI, QIAN JANICE

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/803,578	HWU ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/30/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41 and 94-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41, 94-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/30/07 has been entered.

Claims 1-40, 42-93 have been canceled. Claim 41 has been amended. Claims 94-109 are newly submitted. Claims 41, 94-109 are pending and under current examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of Claims 1, 8, 40, 41, 45, 46, 52, 56, 58, 61, 71, 79, 80, 83, 86, 87, 92 under 35 U.S.C. 102(b) as being anticipated by *Clay et al* (J Immunol 1999;163:507-13), is withdrawn in view of persuasive argument.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41, 94-103, 105, 106, 108, 109 stand or newly rejected under 35 U.S.C. 103(a) as being obvious over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol 1999;162:25-34)

Hwu et al. teaches a method for preparing tumor reactive lymphocytes comprising **a**). providing murine tumor infiltrating lymphocytes (TIL) transduced with a recombinant retroviral vector (Mov-γ) encoding a chimeric receptor reactive with ovarian adenocarcinoma cells in the presence of IL-2 (e.g. the abstract, and column 2, page 3369), wherein the chimeric receptor comprising a single chain variable region from mAbs joined to the Fc receptor γ chain and capable of mediating T cell receptor signal transduction and binding FBP (e.g. column 2, page 3369), and **b**). the transduced TIL cells were co-cultured with syngeneic MC38 colon tumor cells, which results in a large

amount of mIFN-γ production (indicating the TIL cells contain an endogenous T-cell receptor reactive with the syngeneic MC38 cells). The process taught by *Hwu et al* differs from instantly claimed in that the (stimulator) tumor cell in the co-culture is syngenic, not allogenic.

Munz et al. supplemented *Hwu et al.* by establishing that using an allogenic cell as T cell stimulus is comparable to the syngenic/autologous stimulation in obtaining potent tumor reactive CTL cells. *Munz et al.* co-cultured PBL with irradiated allogenic (T2 cells) or syngenic PBL in the presence of IL-2 (left column, page 26), and reported that allogenic APC allows the stimulation of high avidity cytotoxic T cell. *Munz et al.* also taught the need in the art for the allorestricted T cells because the immune system of a cancer patient is often partially destroyed by chemotherapy or factors produced by tumor cells, and under such circumstance, allogenic APCs may be used for tumor antigen-specific T cell activation in immunosuppressed patients (e.g. the paragraph bridging pages 32-33), and concluded with respect to allogenic stimulated T lymphocytes, "SUCH T CELLS MIGHT INDEED BE USEFUL FOR TUMOR IMMUNOTHERAPY" (e.g. abstract).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the preparation process as taught by *Hwu et al.,* with that of *Munz et al.* by co-culturing either syngenic or allogenic APCs with T cells for activation, with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the benefit as taught by *Munz et al.* Given numerous methods known in the art for T cell activation and

expansion, this limitation falls within the bounds of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 104 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol 1999;162:25-34) as applied to claims 41, 94-103, 105, 106, 108, 109 above, and further in view of *Kawakami et al* (USP 5,844,075).

New claim 104 requires that allogeneic:lymphyocyte ratio is about 2:1 to about 5:1, while the cited references do not discuss the ratio. However, such ratio appears to be a routine in the art. For example, *Kawakami et al.* teaches, in the context of expanding antigen-specific T cells, the stimulator:responder cell ratio is between 3:1 to about 10:1 (e.g. § bridging col. 54-55). Here the syngenic/allogeneic cells are the stimulator while lymphocytes are the responder.

Further, considering *Hwu* reference is applicant's own work, and considering the specification is completely silent with regard to discussion about the ratio, the limitation does not appear to be the novel aspect of the claimed invention, and falls within the bounds of optimization, in the absence of evidence to the contrary.

Claim 107 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Hwu et al* (Cancer Res 1995;55:3369-73, IDS), in view of *Munz et al* (J Immunol 1999;162:25-

34) as applied to claims 41, 94-103, 105, 106, 108, 109 above, and further in view of *Raubitschek et al* (USP 6,41,319).

The combined teaching of *Hwu et al* in view of *Munz et al* fails to specify the rapid expansion protocol as recited in claim 107. *Raubitschek et al.* remedies the deficiency by establishing REP was a well-known protocol for lymphocyte expansion (column 14, lines 18-19).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the REP taught by *Raubitschek et al.,* in the preparation process as taught by *Hwu et al.* in view of *Munz et al.* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so because it is one of the routine procedure for lymphocyte expansion. Given the knowledge of the skilled in the art, this limitation falls within the bounds of design choices. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the remarks, the applicant first argues that Hwu does not teach or suggest T cells comprising a tumor reactive chimeric TCR and an *alloreative* endogenous TCR.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

1986). In the instant case, *Hwu* teaches T cells comprising a tumor reactive chimeric TCR and a syngenic reactive endogenous TCR. It is the combined teaching that arrives at the claimed invention, i.e. T cells comprising a tumor reactive chimeric TCR and an alloreative endogenous TCR.

Applicant then argues instant claims requires selecting for T cells with endogenous TCR, whereas Hwu teaches transduction of genes encoding chimeric TCR into T cells eliminates the need to isolate naturally occurring T cells with particular antigen specificity, and thus teaches away from instant claims (pointing to the first three sentences of the Discussion Section).

Applicant's arguments have been fully considered but they are not persuasive. This is because by co-culture with syngenic tumor cells (MC38), *Hwu et al.* effectively selects for T cells with MC38-specific endogenous TCR. The first three sentences of the Discussion Section apparently discuss the advantage of altering T cell specificity with a chimeric TCR, which do not teach away from selecting the endogenous TCR, and said advantage would also apply to instantly claimed chimeric TCR. Hence, *Hwu et al.* does not teach away from instantly claimed invention.

Accordingly, the rejections *supra* stand.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730.

The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on 571-272-0739. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
January 17, 2008